REMARKS

Claims 1-46 are currently pending in the application. Claims 1-14 have been withdrawn from consideration. Applicants have amended Claims 1, 4, 6, 15, 16, 30, 32, and 46. The amendments add no new matter and are fully supported by the specification and claims as originally filed. Claims 15-46 are rejected by the Examiner. Applicants respond below to the rejections set forth in the Office Action mailed May 9, 2007. For the reasons set forth below, Applicants respectfully traverse.

Specification

The Examiner has objected to the specification for containing improper references to trademarks. Applicants have amended the specification to capitalize trademarks, and to refer to generic terminology. Applicants respectfully request withdrawal of the objection in view of the amendments to the specification.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 15-46 under 35 U.S.C. § 112, second paragraph as allegedly failing to particularly point out and distinctly claim the invention. In particular, the Examiner states that the preamble recites a method for verifying the efficiency of a sample preparation, but maintains that "it is not clear if the goal of the preamble is achieved and if so, in what step." *Office Action* at 4. The Examiner also states that the recitation of "a 10 sample of clinical, environmental or alimentary origin" in Claims 28 and 44 render the claims indefinite since it is not clear whether Applicant is suggesting that the sample comprises a total of 10 test samples.

Applicants have amended independent Claims 15 and 32 to recite "wherein detection of said IC DNA is indicative of efficient sample preparation and/or performance of nucleic acid amplification." Independent Claims 15 and 32 provide that the test sample and reagent (which comprises cells or organelles that comprise internal control sequences) is subjected to a sample preparation procedure in order to release, purify and/or concentrate nucleic acids of the reagent and test sample. Amplification and/or detection procedures are preformed on the nucleic acids released from the reagent and the test sample. Detection of IC nucleic acids in a test sample with added reagent that has been subjected to the sample preparation procedure is indicative that the sample preparation procedure efficiently released the nucleic acids of the reagent from the test

sample with added reagent. Detection of IC DNA in a test sample with reagent following the sample preparation and amplification reactions verifies the efficiency of the sample preparation and amplification procedures. Accordingly, it is clear that the recited steps provide a method for verifying the efficiency of sample preparation and amplification and/or detection, as recited in the claims.

Applicants have amended Claims 28 and 44 to delete the term "10" from the claims. The amendment addresses the Examiner's rejection set forth above.

In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of Claims 15-46 under 35 U.S.C. § 112, second paragraph.

General Comment Regarding Art Rejections

As a general comment applicable to many of the prior art rejections, Applicants wish to emphasize the importance of appropriate and verifiable sample preparation in molecular diagnostic assays. Universal sample preparation is currently a major problem in the art, and commercially-viable methods for verifying the quality of sample preparation represents a long-felt need. Verifying sample preparation is not to be confused with providing an internal control in a PCR reaction. The latter is used to indicate whether PCR is proceeding as it should. The former indicates whether the sample has been appropriately prepared.

Rejection Under 35 U.S.C. § 102(b) - Ke et al.

The Examiner has rejected Claims 15, 16, 18-21, 23-29, 31-32, 34-37, and 39-45 under 35 U.S.C. § 102(b) as allegedly being anticipated by Ke et al. According to the Examiner, Ke et al. "teach a method comprising providing a reagent comprising a cell comprising a bacterial cells [*sic*] comprising at least one nucleic acid sequence serving as an internal control target [for- *sic*] sample preparation; adding said reagent into said test sample; [and] submitting said released nucleic acid to amplification or detection," thereby meeting each and every element of Claims 15 and 32. *Office Action* at 5. Applicants respectfully disagree.

Ke et al. do not teach each and every element of Claims 15 and 32, or claims that depend therefrom. Claims 15 and 32 recite a method that involves the steps of providing a reagent selected from "cells, organelles, parasites, cells comprising organelles, cells comprising viral particles, cells comprising parasites, cells comprising bacterial cells or any combination thereof." The reagent is added to a test sample, and the test sample and added reagent is then subjected to a

sample preparation procedure to release, purify and/or concentrate nucleic acids from the test sample and added reagent. Ke et al. teach a plasmid that contains an internal control sequence. The plasmid is propagated in *E. coli* cells. Subsequently, the plasmid DNA is purified from the *E. coli* culture, and linearized. The isolated, linearized plasmid DNA is added to a PCR reaction as an internal control in a PCR assay. Accordingly, Ke et al. do not add a reagent comprising cells or organelles to a test sample, Ke et al. do not process the test sample with added reagent to release, purify and/or concentrate nucleic acids of both the test sample and added reagent, and Ke et al. do not submit released, purified and/or concentrated nucleic acids from the sample preparation step to amplification an/or detection for the amplification and/or detection of both said IC and test sample nucleic acids, as recited in Claims 15, 16, 18-21, 23-29, 31-32, 34-37, and 39-45. As the method of Ke et al. do not teach these steps, it does not provide a means to verify the efficiency of sample preparation. In view of the fact that Ke et al. fail to teach each and every element of the rejected claims, Applicants respectfully request that the Examiner withdraw the rejection under 35 U.S.C. §102(b).

Rejection Under 35 U.S.C. § 102(b) - Saldanha et al.

The Examiner has rejected Claims 15-17, 32 and 33 under 35 U.S.C. § 102(b) as allegedly being anticipated by Saldanha, J. (2001) *J. Clin. Virol.* 20:7-13. According to the Examiner, Saldanha teaches a method comprising providing a reagent comprising a cell comprising a viral particle comprising an internal control sequence, adding the reagent to a test sample, and submitting the released nucleic acids to amplification of detection, thereby meeting each of the limitation of Claims 15 and 32. Applicants respectfully disagree.

Saldanha does not teach each and every element of Claims 15-17, 32 and 33. Specifically, Claims 15-17, 32 and 33 recite the step of "providing a reagent comprising any one of cells, organelles, parasites, cells comprising organelles, cells comprising viral particles, cells comprising parasites, cells comprising bacterial cells, or any combination thereof." Saldanha is a review article that discuses standardization of nucleic acid amplification assays to detect viruses. There is no mention within Saldanha of the use of cells comprising viral particles, or any other of the reagents recited in Applicants' claims as a reagent for an internal control. The Saldanha abstract discusses the use of reagents comprising "lyophilized preparations" of viruses to validate assay runs. *See,* Saldanha, Abstract. These lyophilized reagents are not "cells, organelles,

parasites, cells comprising organelles, cells comprising viral particles, cells comprising parasites, cells comprising bacterial cells, or any combination thereof." Therefore, Saldanha fails to meet each and every limitation of Claims 15-17, 32 and 33. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b).

Rejection Under 35 U.S.C. § 102(a) - Picard et al.

The Examiner has rejected Claims 15-21, 30, 32-34, 36, 37 and 46 under 35 U.S.C. § 102(a) as allegedly being anticipated by Picard et al. (2002) *Drug Disc. Today* 7(2):1092-1101. According to the Examiner, Picard et al. teach a method comprising proving a reagent comprising a cell comprising bacterial cells with an internal control sequence, adding the reagent into a test sample, and submitting released nucleic acids to amplification or detection, and comparing the amplification and/or detection with control reactions to evaluate the efficiency of the sample preparation. *Office Action* at 9. Applicants respectfully disagree.

Picard et al. do not teach each and every limitation of Claims 15-21, 30, 32-34, 36, 37 and 46. Specifically, Picard et al. do not teach adding a reagent that is a cell or organelle harboring internal control sequences to a test sample, and isolating, purifying and/or concentrating the nucleic acids from the test sample with the added reagent as recited in Claims 15 and 32, as well as Claims 16-21, 30, 31, 33-34, 36 and 37. Picard et al. describe internal controls for nucleic acid amplification assays. However, Picard et al. teach that the internal controls are "integrated into the NAT assay, and are designed to verify the efficiency of each amplification and/or detection reaction." Picard et al. are silent regarding the addition of a reagent that comprises cells and/or organelles to a test sample, followed by a step of releasing, purifying and/or concentrating the nucleic acids from the test sample and added reagent. As such, the method described in Picard et al. does not verify the efficiency of test sample preparation, as recited in Applicants' claims. Because Picard et al. fail to teach each of these limitations of Claims 15-21, 30, 32-34, 36, 37 and 46, the reference does not anticipate the claims. Applicants therefore respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(a).

Rejection Under 35 U.S.C. § 103(a) - Ke et al. in view of Kuske et al.

The Examiner has rejected Claims 21 and 37 under 35 U.S.C. § 103(a) as allegedly being unpatentably obvious over Ke et al. in view of Kuske et al. (1998) *Appl. Environ. Microbiol.* 64(7):2463-2472. The Examiner's assertions regarding the teachings of Ke et al. are discussed

above. The Examiner states that Ke et al. teach every limitation of Claims 15 and 32, but that Ke et al. does not teach reagents comprising *Bacillus globigii* spores. However, the Examiner states that Kuske et al. teach a method for determining the efficiencies of a sample preparation for PCR amplification and detection wherein the sample comprises bacterial spores. According to the Examiner, the skilled artisan would have been motivated to modify the method of Ke et al. "to encompass other spore forming bacterial microbes such as *B. globigii* for the benefit of increases [*sic*] sensitivity of PCR detection of environmental samples." *Office Action* at 11. Applicants respectfully disagree.

To establish a *prima facie* case of obviousness, the prior art must teach or suggest all the claim limitations, and there must be a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The cited references do not teach or suggest each and every element of Claims 21 and 37, alone or in combination.

The Examiner's rejection is based on the assertion that Ke et al. teach each and every element of Claims 15 and 32. As discussed above, Ke et al. do not teach the step of adding a reagent comprising cells or organelles to a test sample, and processing the test sample with added reagent to release, purify and/or concentrate nucleic acids of both the test sample and added reagent. Kuske et al. fail to teach subjecting the released, purified and/or concentrated nucleic acids obtained from the sample preparation step to amplification and/or detection. Kuske et al. do not fill the deficiencies of Ke et al. Kuske et al. do not teach adding a reagent comprising *B. globigii* cells comprising an internal control nucleic acid sequence to a test sample, submitting the test sample with added reagent to a sample preparation procedure to release, purify and/or concentrate nucleic acids from the test sample and added reagent, and submitting the released, purified and/or concentrated nucleic acids to amplification and/or detection for the amplification and/or detection of both the IC target and test sample nucleic acids. At most, Kuske et al. teach a method to determine the detection limit of *B. globigii* cells from a soil sample, comprising seeding *B. globigii* cells in soil, preparing nucleic acids from the soil sample, and amplifying *B. globigii* nucleic acids. Kuske et al. do not teach the amplification and/or detection of both internal control nucleic acids and test sample nucleic acids prepared from a sample preparation step, as recited in Applicants' claims. In short, neither Ke et al. or Kuske et al., alone or in combination teach or fairly suggest combining a reagent and test sample, releasing nucleic acids

from the combined reagent and test sample, and amplification and/or detection of nucleic acids of the reagent and the test sample. Since the references do not teach each and every limitation of Claims 15 and 32, alone or in combination, they cannot support a *prima facie* case of obviousness under 35 U.S.C. § 103(a). Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

CONCLUSION

In view of the above amendments and remarks, Applicants respectfully maintain that the claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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